Toxicology of Organic Phosphate Insecticides

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SUMMARY

The development of effective new insecticides has created potential industrial health hazards to people engaged in their manufacture and application, as well as to those with casual exposures. A group of these insecticides known as the organic phosphates is extremely toxic, destroying the enzyme cholinesterase and exerting a cholinergic action on the mammalian animal. A discussion of the origin, chemistry, and pharmacology of these compounds, along with a description of symptoms, diagnosis and treatment of poisoning is presented. Methods of prevention of poisoning and control measures for the safe use of these compounds are described.

INTENSIVE research in the development of new insecticides in the last few years has resulted in products such as DDT, DDD, chlordane and others which have proven to be a boon to agriculture and in the campaign against insect-borne diseases. However, these new compounds, besides being effective insect killers, are also toxic to humans and can be dangerous if improperly handled. Most recently a new group of compounds, the organic phosphates, has come into use and represents a potential threat to human beings.

Hexaethyl tetraphosphate (HETP) was developed in Germany, where it was known as "Bladan" and was considered for possible use in chemical warfare. Tetraethyl pyrophosphate (TEPP), also known under the name of Vapotone and other commercial designations, is the active toxic ingredient in HETP and was independently developed at the University of Chicago a short time ago.[8] Both these compounds are heavy, syrupy liquids freely miscible with water. On contact with moisture they readily hydrolyze and lose their toxicity; hence, unlike DDT, they have little residual action.

A third organic phosphate is parathion (also known as Thiophos, Alkron and by other commercial names) which is a deep brown liquid of low vapor pressure, some samples of which possess a characteristic odor. Chemically it is O, diethyl O, P-nitrophenyl thiophosphate. It is slightly soluble in water but completely miscible in many organic solvents including ethers, alcohols, and animal and vegetable oils. It is stable in a neutral solution but is rapidly hydrolized in the presence of alkalies, including soap. In actual application as an insecticide, the material may be used as a wettable powder or a dust.

The organic phosphates are very effective in the control of a number of different pests. They are being widely used in the control of mites, codling moths, and other insects which may be resistant to DDT and the older insecticides.[7] Application to fruit orchards and other crops is made by a variety of means, including airplane spraying, mechanical spraying from tractors, and hand spraying.

In the period between January 1, 1948, and August 31, 1949, there were 49 cases of organic phosphate poisoning reported to the California State Department of Public Health, Bureau of Adult Health. One case was fatal. Three deaths due to parathion poisoning in other parts of the country were reported by Hamblin in May 1949,[4] and since that time the authors have had reports of two other fatalities outside of California. Faust[3] reported a typical case of tetraethyl pyrophosphate poisoning in September 1949. Poisoning has occurred among people engaged in the manufacture of these materials, in those compounding solutions containing them, in airplane pilots dusting crops, in agricultural workers, and in people inadvertently exposed (one such was a welder who cut into a pipe containing parathion).

PHARMACOLOGY

In experimental animals it has been demonstrated that the organic phosphates are readily absorbed through the intact skin and from the respiratory and digestive tracts.[5] In all reported cases in humans, absorption was through the skin or respiratory tract, and symptoms appeared within a brief period after exposure, indicating rapid uptake by the body. The compounds themselves are only slightly irritating when first applied to the skin, so there is no immediate warning sign as to the potential danger. If splashed in the eye, there is an intense miosis, resulting in temporary blindness.

The principal mode of action of the organic phosphates is the inactivation or destruction of the enzyme cholinesterase, producing a cholinergic action in mammals.[2] The muscarine-like effect is the underlying cause of the multitude of symptoms which have been recorded by various investigators throughout the country.

SIGNS AND SYMPTOMS

Observed cases have varied from those in which symptoms were mild and transient to those in which severe toxemia resulted in death. Early signs and symptoms include headache, nausea, vomiting, diz-

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ziness, cramps, and constriction of the pupils. More severe poisoning is manifested by a feeling of tightness of the chest, diarrhea, difficulty in breathing, fibrillary twitching of the voluntary muscles, convulsions, and coma.

Death in acute poisoning may be due to any one of the following mechanisms:

1. Bronchial constriction with an outpouring of mucous secretions resulting in mechanical asphyxiation.
2. Central nervous system stimulation and eventual irreversible depression.
3. Stimulation and eventual depression of neuromuscular junctions.
4. Accidents occurring as a result of the visual or mental impairment.

Evidence concerning chronic toxicity and cumulative action is incomplete. However, studies are now under way to determine the effect of chronic exposure to dosages below those producing acute effects. It may be that with chronic exposure an irreversible destruction of cholinesterase can be produced. Experimental animals receiving sublethal doses have survived with no residual damage, presumably because they were able to reproduce enough cholinesterase to replace the amount destroyed by the insecticide.[6] However, further studies on this point are necessary.[1]

At present, diagnosis of intoxication with one of these compounds depends mainly on an awareness of the syndrome and on a high index of suspicion in areas where the chemicals are being used. Any person who may have come into contact with an insecticide, complaining of "blindness," blurred vision, headache, tightness of the chest or any other symptom listed above, should be suspected of acute organic phosphate intoxication. A laboratory finding of reduced cholinesterase activity in the plasma or erythrocytes is confirmatory evidence. However, interpretation of blood cholinesterase levels is difficult.

TREATMENT

Atropine is a specific therapeutic agent against the parasympathetic stimulation. Large doses (1 to 2 mg.) should be administered early and repeated frequently as indicated by the clinical picture. Postural drainage, and suction if available, should be used to remove the excess bronchial secretions and maintain a patent airway. Artificial respiration should be employed if breathing has ceased, and the concomitant use of oxygen may be life-saving.

The following reports are presented to illustrate the signs and symptoms of the disease, as well as the diversity of occupational exposures that have resulted in organic phosphate poisoning:

CASE REPORTS

A 31-year-old white male entomologist, employed by an agricultural experimental station, had been working with parathion intermittently for four months. One morning he arrived at an orchard shortly after 9 o'clock and took charge of the application of parathion which was already in progress. Fruit trees were being sprayed with a mixture containing 2 pounds of parathion (a 25 per cent wettable powder) per 100 gallons of water at the rate of 25 gallons per tree. The patient ran the sprayer while an assistant operated the tank and weighed and measured the ingredients. The sprayer had to be refilled about every 15 minutes, and at the refilling the patient added the ten pounds of powder containing parathion to the tank as the water was being pumped in. During the operation of the sprayer he was constantly exposed to drizzle of the spray. During the morning, he wore no protective clothing or mask other than wrist-length gloves. At noontime he reported to other personnel on the job that everything had proceeded satisfactorily but that he had a headache. In answer to specific inquiries he assured his co-workers that his headache was not severe and probably of no consequence. He went home to lunch and upon returning he was wearing a pair of coveralls in addition to cap, boots and gloves. At 3:25 the manager of the orchard visited the operations and had a conversation with the patient, who in no way indicated that he was aware of any reaction to the material.

The spray operation continued until approximately 4:05 p.m., at which time the patient informed his assistant that he felt dizzy. A few minutes later, while the assistant was cleaning the equipment, the patient became nauseated and vomited. He at first rejected a suggestion that he leave the orchard, but shortly thereafter he got into his car and started to drive home. He drove about a quarter of a mile and again became nauseated. He asked a young man to drive him home and arrived at his house at about 4:45 p.m. and told his wife that he was ill from parathion. He asked her to call a physician and ambulance and to instruct the ambulance to bring an oxygen tent. In the meantime, after help in undressing, he bathed. The physician arrived shortly after 5:00 p.m. and pronounced the patient dead at approximately 5:05 p.m. At no time during his brief illness did the patient receive atropine.

Autopsy did not reveal any other contributing information as to the cause of death, and it was attributed to poisoning by parathion. A postmortem specimen of blood showed no cholinesterase activity and contained one part of parathion per million parts of blood.

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On July 8, 1949, at 8 a.m., three picking crews of 30 men each went into orchards to pick fruit. Two crews were assigned to blocks in the orchard which had been sprayed on June 27, 1949, with parathion spray powder, enough to give 2½ pounds of parathion per acre. The other crew went to a block sprayed on an earlier date.

The day became hot and sultry, with no breeze; the temperature was between 90° and 100°F. Between 12:30 p.m. and 8 p.m. 22 of the pickers working in the most recently sprayed blocks felt ill and quit work to lie down. Most of the men began to vomit. All 22 were taken to the nearest hospital where it was noted that they all had headache, pallor, nausea, vomiting and weakness, and that two or three complained of twitching of arm and leg muscles. They were all given 0.6 mg. of atropine sulfate intramuscularly. In 20 to 30 minutes all improved and vomiting ceased. Ten of the men were permitted to go home that evening, and the remainder who stayed overnight for observation were released the next morning.

Results of urinalysis in all cases were normal. In all cases there was a slight decrease in erythrocyte count and hemoglobin content, while leukocytes numbered between 14,000 and 20,000. Because of lack of facilities, blood cholinesterase determinations were not made.

Most of the men had taken their own lunches from home. Three or four had eaten at the mess hall provided in the orchard. Some had eaten pears from the orchard and others

had not; some had drunk from new containers and some from old containers of water. There was no evidence of any common food or any common source of water supply which was consumed by all of the men. The diagnosis in all cases was acute parathion poisoning caused by inhalation of vapors resulting from spray residue remaining from the spraying which had been done 11 days previously.

Reports of the remaining cases are presented in tabular form.

PREVENTION

Poisoning by this compound can be prevented if proper attention is given to safe methods of handling it and if all persons concerned appreciate its extreme toxicity. All contact with the bare skin must be avoided and natural rubber gloves must be worn when handling parathion. If any of the material gets on the skin it should be thoroughly and

Summary of Data Regarding Cases of Parathion Poisoning Reported to the California State Department of Public Health January 1, 1948, to August 31, 1949

Date	Type of Exposure	Signs and Symptoms	Remarks
1948	Spraying oranges with HETP.	Miosis, with partial loss of vision for 72 hours.	
1948	Spraying oranges with HETP.	Miosis, with partial loss of vision for 8 hours.	
1948	Pilot spraying from airplane with HETP. Refilled hopper several times.	Crashed. Had complained of poor vision during reloading.	Cause of crash not certain but believed to be due to miosis.
1948	Spraying nursery with HETP.	Pupillary constriction for 12 hours, tightness of throat.	
1948	Spraying citrus orchard with HETP and TEPP.	Pupillary constriction. Pulmonary congestion. Pharyngitis.	
1948	Spraying nursery and fruit trees with HETP and TEPP.	Pupillary constriction. Dyspnea.	
1948	Spraying field crop with TEPP.	Miosis; tunnel vision; lacrimation; tightness of chest. Diarrhea.	
1948	Spraying berries from helicopter with TEPP.	Miosis lasting 72 hours. Constriction of chest.	
1948	10-year-old, by observing pest control operator apply TEPP under and around house.	Headache; miosis; nausea; vomiting; muscular twitching. Hospitalized 40 days.	
1948	Smoking orchard with TEPP.	Tracheitis.	
8-25-49	Spraying beans with TEPP.	Substernal burning and tightness.	
8-12-48	Spraying beans with TEPP.	Dizziness, nausea, vomiting, tightness of chest.	
7- 1-49	Spraying from helicopter with TEPP.	Helicopter crashed. Pilot had pinpoint pupils lasting 4 days.	
10-15-48	Spraying with parathion.	Headache, weakness, nausea, perspiration.	
6-27-49	Mixed 15 per cent parathion powder with water and delivered to sprayers. Operated nurse rig.	Dizziness, nausea, vomiting, abdominal cramps, perspiration. Dyspnea; apprehension. Miosis. Auricular fibrillation.	Recovered with treatment with atropine, oxygen, calcium gluconate.
6-30-49	Mixed 15 per cent parathion powder with water and delivered to sprayers. Operated nurse rig.	Nausea, vomiting, miosis, dyspnea. Cyanosis, loss of consciousness. Fibrillary twitching of voluntary muscles.	Recovered with treatment with atropine, oxygen, calcium gluconate.
12- 3-48	Spraying with 1 lb. 15 per cent parathion—100 gallons of water. Spray got on face and chest.	Nausea. Tightness of chest. Heaviness of arms.	Myocardial infarction suspected but EKG normal.
Sept. 1948	Spraying with parathion from 6 a.m. to 2 p.m. on very hot day.	Started at 4 p.m. on day of spraying. Headache; miosis; nausea; vomiting; muscle spasm of legs; convulsions; coma.	Hospitalized five days. Recovered with atropine treatment. Loss of 20 lbs. weight.
8- 6-49	Pruning trees which had been sprayed with parathion 7 days earlier.	Weakness; nausea; vomiting. Hypotension (80/50); bradycardia. Athetoid movements. Pain in right hand.	Good response to atropine.
4- 6-49	Female employee packaging 25 per cent wettable powder parathion in a chemical plant.	Became ill at home several hours after exposure. Chest pain; diarrhea; weakness.	Good response to atropine. Low plasma cholinesterase activity during illness.

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Date	Type of Exposure	Signs and Symptoms	Remarks
June, 1949	Spraying with parathion.	Headache; nausea; vomiting; abdominal cramps; dyspnea; cough; frothy sputum.	
May, 1949	Welding and cut into a pipe containing parathion.	Onset within ten minutes; nausea; vomiting; vertigo; headache.	Hospitalized one day.
Aug., 1949	Had sprayed with parathion, HETP, TEPP, and other insecticides intermittently for 2½ years. Mixed sprays and weighed out wettable powder.	Headache; diarrhea; nausea; vomiting; anorexia.	Insidious onset. Low plasma cholinesterase.
7-27-49	Night superintendent in plant that packages parathion.	Nausea; vomiting; headache; following packaging of parathion.	
8-12-49	Crop dusting with parathion.	Dry skin; nausea; chest pain; pallor and apprehension.	
6-30-49	Spraying crops with parathion.	Nausea; salivation; perspiration.	
9-15-49	Foreman in nursery where parathion was sprayed.	Nausea; myalgia; miosis; dyspnea, diarrhea.	Good response to atropine.
7- 8-49	22 pickers working in an orchard that had been sprayed on June 27, 1949. Very hot day. Onset of symptoms 4½ to 12 hours after picking started.	Pallor; nausea; vomiting; sweating; weakness. W.B.C. elevated. R.B.C. lowered. Urinalyses negative.	Remarkably rapid response to atropine.
8-23-49	Sprayed fruit grove with parathion all day. Drove tractor and made up parathion solution.	Headache; vertigo; nausea; vomiting. Death occurred 8 hours after starting work.	Received no treatment. Dead on arrival of M.D. Postmortem blood had no cholinesterase activity.

quickly washed off with copious amounts of soap and water. Workmen should be provided with freshly laundered coveralls and should wear fresh clothing each day, including socks and underwear. In addition, sprayers or others who are likely to be drenched with the chemical should be provided with a cellophane cape and hat or other liquid-repellent garment, as ordinary clothing will prove to be merely a reservoir for further absorption. Inhalation should be avoided by use of a chemical cartridge respirator, full face-piece type equipped with GMC-1 canister.* Workers should bathe with soap and water after using the material, and contamination of food and tobacco should be avoided. An added safeguard is to avoid prolonged exposure. This may be accomplished by rotating workers on different job assignments so that no one worker deals with the organic phosphates day after day for a long period.

The question has arisen as to the wisdom of providing atropine to exposed workers, to be taken if symptoms of poisoning occur. The proponents of this procedure argue that it may be life-saving, while others feel that it would lead to self-medication in many cases where symptoms were due to something other than organic phosphate poisoning. A practical procedure may be to leave a small supply of atropine with a foreman or other responsible person, who should be instructed to telephone a physician should symptoms develop in any exposed workers. He could then be informed whether or not to administer the atropine while waiting for the doctor's arrival.

To date, no cases of poisoning due to ingestion of food sprayed with these materials have occurred. It is recommended that there be at least a 30-day interval between application of parathion and harvesting of the crop. If this is heeded, it is believed that there is no danger to the consumer.

*Sprayers should check with their local health department or department of agriculture for the best kind of respirator.

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